Priority Claim

In the Office Action, the Examiner indicates that the claims of the instant application have not been granted the benefit of priority to parent application U.S. Serial No. 08/635,344, filed April 19, 1996 (Office Action, page 3). The Examiner states that the parent application did not disclose the sequence comprising SEQ ID NO:14 of independent claim 10 of the instant application.

Applicants respectfully traverse these statements. Applicants note that the generic sequence of SEQ ID NO:14 is not under examination in the instant application. As a result of the restriction/election requirement set forth by the Examiner in the Office Action mailed May 23, 2000, Applicants were required to elect a specific sequence for examination. Applicants elected the species YLVVVGADGV via telephone on September 27, 2000.

Applicants note that the sequence YLVVVGADGV was disclosed in the parent application as SEQ ID NO:11. See page 9, lines 13-14 of the parent application as originally filed. Because the elected claims of the application are directed to the species YLVVVGADGV, and because the sequence YLVVVGADGV was disclosed in parent application U.S. Serial No. 08/635,344, filed April 19, 1996, Applicants are rightfully entitled to claim priority to for the claims of the instant application. Applicants respectfully request recognition of the priority claim of the instant application.

35 U.S.C. §112, second paragraph

Claim 34 stands rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention (Office Action, page 2). The Examiner states that RIBI Detox™ is used to

identify a pharmaceutical composition in the claim, making the identification/description of the composition indefinite (Office Action, page 2). The Examiner has suggested that Applicants delete the trademark/trade name RIBI Detox™, and replace it with a description of the RIBI Detox™ components, i.e., mycobacterial cell wall extracts, monophosphoryl lipid A, etc. (Office Action, page 3).

As a result of this Amendment, claim 34 has been amended to delete the trademark/trade name RIBI Detox™, and replace it with description of an adjuvant comprising mycobacterial cell wall skeleton and monophosphoryl lipid A. In addition, the specification has been amended to include description of RIBI Detox™ comprising mycobacterial cell wall skeleton and monophosphoryl lipid A. No new matter is added by these amendments. The subject matter of the amendments is fully supported by, *inter alia*, Example 1 in the application as originally filed, and by the known, defined, and inherent components of RIBI Detox™. Withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

35 U.S.C. §103(a): Claims 10-15, 27, and 32

Claims 10-15, 27 and 32 stand rejected under 35 U.S.C. §103(a) as being obvious over Van Elsas et al. (1995) or Gjertsen et al. (1996) in view of Ruppert et al. (1993) or U.S. Patent No. 5,861,372 (1999) (Office Action, pages 3-4). The Examiner relies on peptides reported by the following references:

- Van Elsas et al. report a peptide KLVVVGADGV (5-14, 12Asp *ras*); (page 391, Table I);
- Gjertsen et al. report a peptide KLVVVGADGVGKSALTI (5-21, 12Asp *ras*); (page 451, Table 1);
- Ruppert et al. report a 10-mer peptides containing various residues (X1 = A, Y, F, or W;

X2 = L or M; X3 = L, V, I, or M; X4 = G; X5 = no preference; X6 = G; X7 = no preference; X8 = Y, F, W, L, V, I, or M; X9 = no preference; X10 = L, V, or I (page 932, figure 3); and

- The '372 patent reports angiostatin and angiostatin-related peptides modified with a K or Y residue (column 22, lines 24-28).

The Examiner states that Applicants' peptide sequence YLVVVGADGV (5-14, 1Tyr-12Asp *ras*) is obvious over the cited combination of references. Applicants respectfully traverse this rejection under 35 U.S.C. §103(a).

Van Elsas et al. peptide KLVVVGADGV (5-14, 12Asp *ras*)

It is respectfully asserted that the Van Elsas et al. reference provides no motivation for one in the art to use the KLVVVGADGV (5-14, 12Asp *ras*) peptide. In fact, the Van Elsas et al. reference acts to discourage the use of the KLVVVGADGV (5-14, 12Asp *ras*) peptide. Applicants point to Table I. Table I shows that the peptide KLVVVGADGV (5-14, 12Asp *ras*) showed poor binding to HLA-A*02021 (Table I). In contrast, the CLLDILDTAGL (51-61, 61Leu *ras*) peptide showed excellent binding to HLA-A*02021 (Table I). Comparison of the F.I. values indicates that the binding of the KLVVVGADGV (5-14, 12Asp *ras*) peptide to HLA-A*02021 was nearly an order of magnitude less than the CLLDILDTAGL (51-61, 61Leu *ras*) peptide (Table I).

Accordingly, Van Elsas et al. used the CLLDILDTAGL (51-61, 61Leu *ras*) peptide in the remainder of their experiments. Van Elsas et al. did not perform any further experiments on the KLVVVGADGV (5-14, 12Asp *ras*) peptide. One may conclude that Van Elsas et al. believed that the KLVVVGADGV (5-14, 12Asp *ras*) peptide was unsuitable for CTL response induction studies. In this way, the results reported by Van Elsas et al. would act to discourage the use of

the KLVVVGADGV (5-14, 12Asp *ras*) peptide. At the very least, Van Elsas et al. provide no motivation for a person in the art to select the KLVVVGADGV (5-14, 12Asp *ras*) peptide for further analysis. Accordingly, a person in the art would lack motivation to use the Van Elsas et al. peptide to create Applicants' invention of YLVVVGADGV (5-14, 1Tyr-12Asp *ras*).

In contrast to the findings of Van Elsas et al., Applicants clearly demonstrate that the KLVVVGADGV (5-14, 12Asp *ras*) single-mutant peptide binds to HLA-A2 (see Table 7). The Van Elsas et al. reference effectively tells those in the art not to use the KLVVVGADGV (5-14, 12Asp *ras*) peptide; as it does not bind to HLA-A2 (Table I). Conversely, Applicants' teach those in the art to use the KLVVVGADGV (5-14, 12Asp *ras*) peptide, as it binds to HLA-A2 (Table 7) and induces a CTL response (Figures 4 and 5). Applicants further teach that the KLVVVGADGV (5-14, 12Asp *ras*) peptide can be modified to produce the YLVVVGADGV (5-14, 1Tyr-12Asp *ras*) peptide to enhance the CTL response (Figure 11).

MPEP §2141.03 states "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)" (emphasis in original). Accordingly, the Examiner is required to consider the poor binding of the KLVVVGADGV (5-14, 12Asp *ras*) peptide reported by Van Elsas et al. Then, the Examiner is required to step backwards in time into the shoes worn by the person in the art when Applicants' invention was unknown and just before it was made (MPEP §2142). It is then that it becomes apparent that Van Elsas et al. provide no motivation to use or modify the KLVVVGADGV (5-14, 12Asp *ras*) peptide, and actually lead away from Applicants' invention of the sequence YLVVVGADGV (5-14, 1Tyr-12Asp *ras*).

Notably, where a claimed invention teaches away from other references in the field, this is per se proof of lack of prima facie obviousness. *In re Dow Chemical Co.,* 837 F.2d 469, 5 USPQ 1529 (Fed. Cir. 1988); *In re Fine,* 837 F.2d 1071, 5 USPQ 1596 (Fed. Cir. 1988); *In re Nielson,* 816 F.2d 1567, 2 USPQ2d 1525 (Fed. Cir. 1987). The Federal Circuit Court has held that where an inventor proceeds contrary to the accepted wisdom, "[t]his is strong evidence of nonobviousness" and other rebuttal evidence is not required. *In re Hedges,* 783 F.2d 1038, 1041, 228 USPQ 685, 687 (Fed. Cir. 1986).

In addition, the Examiner is required to consider any teaching or suggestion in the cited reference of a preferred species that is significantly different in structure from the claimed species, as such teaching may weigh against selecting the species and thus against a determination of obviousness (MPEP §2144.08(c)). Therefore, it must taken into consideration that the CLLDILDTAGL (51-61, 61Leu *ras*) peptide is the preferred species of peptide reported by Van Elsas et al. Moreover, the CLLDILDTAGL (51-61, 61Leu *ras*) peptide is dramatically different in sequence and structure from Applicants' invention YLVVVGADGV (5-14, 1Tyr-12Asp *ras*).

It is therefore respectfully asserted that, 1) because Applicants' invention *teaches away* from the showing of Van Elsas et al., and 2) the preferred peptide species in Van Elsas et al. is *structurally different* from the claimed species of the invention, the claims are not obvious over Van Elsas et al., either alone or in combination with the other references.

Gjertsen et al. peptide KLVVVGADGVGKSALTI (5-21, 12Asp *ras*)

It is respectfully asserted that the Gjertsen et al. reference provides no motivation to use the KLVVVGADGVGKSALTI (5-21, 12Asp *ras*) peptide. In reality, the Gjertsen et al.

reference acts to discourage persons in the art from using the KLVVVGADGVGKSALTI (5-21, 12Asp *ras*) peptide. Applicants point to Table III. For patient 4 and patient 5, immunization with the KLVVVGADGVGKSALTI peptide (5-21, 12Asp *ras*) resulted in no observed immunological response (Table III). For patient 3, immunization the KLVVVGADGVGKSALTI peptide (5-21, 12Asp *ras*) resulted in a strong, non-specific immune response to both KLVVVGADGVGKSALTI (5-21, 12Asp *ras*) and KLVVVGAGGVGKSALTI (5-21, wild-type *ras*). None of the patients immunized with the KLVVVGADGVGKSALTI peptide (5-21, 12Asp *ras*) produced a peptide-specific response (Table III).

A non-specific immune response to a wild-type, endogenous protein is typically considered a deleterious side-effect for a vaccine. Thus, the results of Gjertsen et al. show that the KLVVVGADGVGKSALTI (5-21, 12Asp *ras*) peptide is either inefficacious or deleterious in humans. In this way, Gjertsen et al. act to discourage the KLVVVGADGVGKSALTI (5-21, 12Asp *ras*) peptide. At the very least, Gjertsen et al. provide no motivation for a person in the art to use the KLVVVGADGVGKSALTI (5-21, 12Asp *ras*) peptide. Accordingly, a person in the art would have no motivation to use the Gjertsen et al. peptide to create Applicants' invention of YLVVVGADGV (5-14, 1Tyr-12Asp *ras*).

In contrast to the findings of Gjertsen et al., Applicants' disclose that the KLVVVGADGV (5-14, 12Asp *ras*) single-mutant peptide produces a peptide-specific CTL response (page 45, lines 4-6). The Gjertsen et al. reference effectively tells those in the art not to use the KLVVVGADGVGKSALTI (5-21, 12Asp *ras*) peptide; as it results in a non-specific immune response. Conversely, Applicants' teach those in the art to use the KLVVVGADGV (5-14, 12Asp *ras*) peptide, as it produces a peptide-specific immune response (page 45, lines 4-6).

Applicants further teach that the KLVVVGADGV (5-14, 12Asp *ras*) peptide can be modified to produce the YLVVVGADGV (5-14, 1Tyr-12Asp *ras*) peptide to enhance the CTL response (Figure 11).

Applicants again note that a prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention (MPEP §2141.03; *Gore v. Garlock*, 721 F.2d 1540). Accordingly, the Examiner is required to consider the inefficacy and side-effects of the KLVVVGADGVGKSALTI (5-21, 12Asp *ras*) peptide reported by Gjertsen et al. In addition, the Examiner is required to step backwards in time into the shoes worn by the person in the art when Applicants' invention was unknown and just before it was made (MPEP §2142). From this viewpoint, it becomes clear that the Gjertsen et al. reference provides no motivation to use or modify the KLVVVGADGVGKSALTI (5-21, 12Asp *ras*) peptide, and actually leads away from Applicants' invention of the sequence YLVVVGADGV (5-14, 1Tyr-12Asp *ras*).

It is further noted that, where a claimed invention teaches away from other references in the field, this proves, *per se*, lack of prima facie obviousness. *In re Dow Chemical,* 837 F.2d 469; *In re Fine,* 837 F.2d 1071; *In re Nielson,* 816 F.2d 1567. According to the Federal Circuit, research that proceeds contrary to the accepted wisdom is strong evidence of nonobviousness, and no other rebuttal evidence is required. *In re Hedges,* 783 F.2d at 1041.

Applicants respectfully assert that, because Applicants' invention *teaches away* from the showing of Gjertsen et al., the claims are not obvious over Gjertsen et al., either alone or in combination with the other references.

Ruppert et al. peptide (10-mer $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$, where X1 = A, Y, F, or W; X2 = L or M; X3 = L, V, I, or M; X4 = G; X5 = no preference; X6 = G; X7 = no preference; X8 = Y, F, W, L, V, I, or M; X9 = no preference; X10 = L, V, or I)

It is respectfully asserted that the Ruppert et al. reference provides no motivation to create Applicants' exact sequence YLVVVGADGV (5-14, 1Tyr-12Asp *ras*). For a 10-mer peptide, Ruppert et al. use four possible amino acids at position 1 (A., Y, F, and W), and eight possible amino acids at position 8 (M, I, V, L, W, F, and Y; see above). Ruppert et al. fail to teach which specific residue should be present at position 1, or which specific residue should be at position 8. This teaching is not provided by the other references. In fact, the Van Elsas et al. and Gjertsen et al. references contradict the Ruppert et al. reference regarding which residues should be used at positions 1, 4, and 8 (discussed in detail below). Accordingly, none of the cited references, alone or in combination, teach or suggest Applicants' exact sequence YLVVVGADGV (5-14, 1Tyr-12Asp *ras*).

Applicants note that all inventions are necessarily the combination of known elements or steps and that the inspiration to select and combine is the creative act. *Reeves Instruments v. Beckman Instruments*, 444 F.2d 263, 270, 170 USPQ 74 (9th Cir. 1971); *Republic Industries v. Schlage Lock, Co.*, 592 F.2d 963, 200 USPQ 769 (7th Cir. 1979). For elements that can be combined in a myriad of permutations, "[i]t is the act of *selection* which is the invention" (emphasis added). *B.G. Corp. v. Walter Kiddle & Co.*, 79 F.2d 20, 22, 26 USPQ 288 (2d Cir. 1935). Amino acids may be thought of as elements that are combined in different ways to create different peptides. Applicants' invention includes the exact combination of amino acids to create the YLVVVGADGV (5-14, 1Tyr-12Asp *ras*) peptide. Notably, none of the cited references, alone or in combination, teach or suggest Applicants' exact sequence YLVVVGADGV (5-14,

1Tyr-12Asp *ras*).

For obviousness, the references themselves must suggest the desirability of making the exact sequence YLVVVGADGV (5-14, 1Tyr-12Asp *ras*) without the slightest recourse to the teachings of the instant application. Without such independent suggestion, the references are to be considered merely to be inviting unguided and speculative experimentation, which is not the standard for determining obviousness. *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991); *In re Laskowski*, 871 F.2d 115, 117, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989); *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988).

It is also pointed out that Applicants' results regarding the YLVVVGADGV (5-14, 1Tyr-12Asp *ras*) peptide are surprising and unexpected in view of the results of Ruppert et al. Ruppert et al. indicate that, for 10-mer peptides, D is contraindicated at position 8 (compare to Applicants' peptide $Y_1L_2V_3V_4V_5G_6A_7\mathbf{D_8}G_9V_{10}$). Ruppert et al. state "the most detrimental effects [on HLA-A2.1 binding] were observed with charged amino acids" (page 932). Ruppert et al. found that none of the synthetic 10-mers that bound to HLA-A2.1 contained D at position 8 (Figure 2B). Based on their results, Ruppert et al. concluded that D at position 8 was strongly associated with poor binding to HLA-A2.1 (Figure 3). D at positions 1 and 3 was also strongly associated with poor binding to HLA-A2.1 (Figure 3). Accordingly, Ruppert et al. designated D an "unfavored residue".

Importantly, Ruppert et al. found that peptides carrying both one favored residue and one or more unfavored residues showed poor binding or no binding to HLA-A2.1 (page 934). This strongly suggested that unfavored residues caused a dominant negative effect on binding, which

could not be overcome by the addition of favored residues. Ruppert et al. noted that "[a] similar dominance of negative effects of charged amino acid substitutions on peptide binding has been implicated by Boehncke et al. (1993) in a murine class II system and by our own group in the DR4W4 system (Sette et al., 1993)" (page 935).

In view of the results of Ruppert et al., Applicants' results are surprising and unexpected. In particular, Applicants teach that the CTL activity of the YLVVVGADGV (5-14, 1Tyr-12Asp *ras*) peptide is higher than the CTL activity of the KLVVVGAGGV (5-14 wild-type *ras*) peptide (Figure 11). Yet, the YLVVVGADGV peptide has 5 favored residues (Y1, L2, V3, G6, and V10) and 1 unfavored residue (D8). In contrast, the KLVVVGAGGV peptide contains 4 favored residues (L2, V3, G6, and V10) and no unfavored residues. In view of Ruppert et al., a person in the art would predict that the unfavored residue of the YLVVVGADGV would have a dominant negative effect on its HLA-binding, and produce low CTL activity. Applicants' results show that, in fact, the opposite is true (Figure 11).

Thus, Applicants' teaching regarding the YLVVVGADGV (5-14, 1Tyr-12Asp *ras*) peptide is surprising and unexpected in view of Ruppert et al. Under 35 U.S.C. §103, the Examiner is required to consider objective evidence of non-obviousness, such unexpected results. MPEP *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966); *Allen Archery, Inc. v. Browning Mfg. Co.*, 819 F.2d 1087, 1092, 2 USPQ2d 1490, 1493(Fed. Cir. 1987) *Miles Labs., Inc. v. Shandon, Inc.*, 997 F.2d 870, 877, 27 USPQ2d 1123, 1128 (Fed. Cir. 1993). The Examiner must consider all of the advantages, properties, utilities, and unexpected results flowing from the claimed invention, as they are part of the invention as a whole. *In re Chupp*, 816 F.2d 643, 2 USPQ2d 1437 (Fed. Cir. 1987); *Fromson v. Advance Offset Plate*, 755 F.2d

1549, 225 USPQ 26 (Fed. Cir. 1985); *In re Piasecki*, 745 F.2d 1468, 223 USPQ 785 (Fed. Cir. 1984); *Carl Schenck, A.G. v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983).

It is respectfully asserted that, 1) because Ruppert et al. and the other references fail to teach the *exact, claimed sequence* YLVVVGADGV and 2) Applicants' results are *unexpected an surprising* in view of the Ruppert et al. reference, the claims are not obvious over Ruppert et al., either alone or in combination with the other references.

'372 patent angiostatin and angiostatin-related peptides

It is respectfully asserted that the '372 patent provides no motivation to create Applicants' sequence YLVVVGADGV (5-14, 1Tyr-12Asp *ras*). In fact, the '372 patent leads those in the art away from Applicants' invention. First, the '372 patent reports angiostatin and angiostatin peptides. Angiostatin shares no significant sequence homology with the *ras* peptides of Applicants' invention. Second, the angiostatin peptides are notably larger than the claimed *ras* peptides. The '372 patent describes peptides encompassing amino acid 98 through amino acid 812 of murine angiostatin (column 10, lines 2-10). Thus, the '372 patent uses 714-mer peptides, whereas Applicants' invention encompasses 10-mer peptides.

As before, Applicants note that a prior art reference must be considered in its entirety, including portions that would lead one away from the claimed invention (MPEP §2141.03; *Gore v. Garlock*, 721 F.2d 1540, 220 USPQ 303). Accordingly, the Examiner is required to consider the large size and dramatically different sequence of the angiostatin peptides reported by the '372 patent. In addition, the Examiner is required to step backwards in time into the shoes worn by the person in the art when Applicants' invention was unknown and just before it was made (MPEP §2142). From this viewpoint, it becomes clear that there is no motivation to modify the

angiostatin peptides of the '372 patent to create Applicants' sequence YLVVVGADGV (5-14, 1Tyr-12Asp *ras*).

The Examiner is also required to consider any teaching or suggestion in the cited reference of a preferred species that is significantly different in structure from the claimed species, as such teaching may weigh against selecting the species and thus against a determination of obviousness (MPEP §2144.08(c)). Therefore, it must be taken into consideration that the angiostatin peptides are the preferred species of peptide reported by the '372 patent. Moreover, the angiostatin peptides are dramatically different in sequence and structure from Applicants' invention YLVVVGADGV (5-14, 1Tyr-12Asp *ras*).

In addition, while the '372 patent suggests the addition of K or Y residues to an angiostatin peptide, it fails to teach which specific position should contain K or Y. Contrary to the Examiner's statement, the '372 patent does not specifically state that a K or Y should be used at the first position of a peptide Y (see column 22, lines 24-28). Accordingly, a K or Y residue could be added anywhere along the length of an angiostatin peptide. As angiostatin peptides are 714 amino acids in length, the K or Y residue could be added to any one of 714 different positions. Moreover, the '372 patent fails to indicate which specific residue should be used, i.e., whether K or Y is preferred. The Van Elsas et al. and Gjertsen et al. references use K at position 1. However, this is distinguished from Applicants' invention, which contains a Y at position 1. Accordingly, none of the cited references, alone or in combination, teach or suggest Applicants' exact sequence, YLVVVGADGV (5-14, 1Tyr-12Asp *ras*).

Applicants' invention encompasses the exact combination of amino acids to create the YLVVVGADGV (5-14, 1Tyr-12Asp *ras*) peptide. Where elements (e.g., amino acids) can be

combined in an endless number of permutations, it is the selection of an exact combination that is the invention. *B.G. Corp. v. Walter Kiddle,* 79 F.2d 20, 22, 26 USPQ 288. None of the cited references, alone or in combination, teach or suggest Applicants' exact sequence YLVVVGADGV (5-14, 1Tyr-12Asp *ras*). Without such suggestion, the references are to be considered merely to be inviting unguided and speculative experimentation. This not the standard for determining obviousness under 35 U.S.C. §103. *Amgen v. Chugai,* 927 F.2d 1200; *In re Laskowski,* 871 F.2d 115, 117; *In re Dow Chemical.,* 837 F.2d 469, 473.

Applicants therefore respectfully assert that, 1) because the '372 patent *leads away* from Applicants' invention; 2) the preferred peptide species in the '372 patent is *structurally different* from the claimed species of the invention; and 3) the '372 patent and the other references fail to teach the *exact, claimed sequence* YLVVVGADGV, the claims are not obvious over the '372 patent, either alone or in combination with the other references.

Conflicts among the primary references

The reports of Van Elsas et al. and Ruppert et al. are in conflict. The Van Elsas et al. peptide KLVVVGADGV (5-14, 12Asp *ras*) contained 4 favored residues recommended by Ruppert et al. (L2, V3, G6, and V10) but showed *poor binding* to HLA-A*02021 (Table I). In contrast, the Van Elsas et al. CLLDILDTAGL (51-61, 61Leu *ras*) peptide contained only 2 favored residues recommended by Ruppert et al. (L2 and L3) but showed *excellent binding* to HLA-A*02021 (Table I). Thus, the findings of Van Elsas et al. contradict the findings of Ruppert et al. Accordingly, a person in the art would have no motivation to combine the Van Elsas et al. and Ruppert et al. references to create Applicants' peptide sequence

YLVVVGADGV (5-14, 1Tyr-12Asp *ras*).

Further, there is no suggestion in the art for how to resolve the sequence differences between the peptides reported by Van Elsas et al. and Ruppert et al. For a 10-mer peptide, at position 1, the Van Elsas et al. peptide contained K, whereas Ruppert et al. recommended A, Y, F, or W. At position 4, the Van Elsas et al. peptide contained V, whereas Ruppert et al. recommended G. At position 8, the Van Elsas et al. peptide contained D, whereas Ruppert et al. recommended Y, F, W, L, V, or M. Without further guidance, a person in the art would not know whether to employ the residues used by Van Elsas et al., or any one of the residues recommended by Ruppert et al. No specific guidance for selecting an exact sequence is provided by the cited references, or elsewhere in the art. Accordingly, a person in the art would not know how to reconcile the sequence conflicts between the Van Elsas et al. and the Ruppert et al. peptides to achieve the exact sequence YLVVVGADGV (5-14, 1Tyr-12Asp *ras*) that is Applicants' invention.

Similarly, there is no suggestion in the art for how to resolve the sequence differences between the peptides reported by Gjertsen et al. and Ruppert et al. At position 1, the Gjertsen et al. peptide contained K, whereas Ruppert et al. suggested A, Y, F, or W. At position 4, the Gjertsen et al. peptide contained V, whereas Ruppert et al. suggested G. At position 8, the Gjertsen et al. peptide contained D, whereas Ruppert et al. suggested Y, F, W, L, V, or M. In addition, Gjertsen et al. used a 17-mer peptide, while Ruppert et al. used only 9-mer and 10-mer peptides. Without additional guidance, a person in the art would not know whether to employ the residues used by Gjertsen et al., or any one of the residues suggested by Ruppert et al. Further, a person in the art would not know whether to use a 17-mer peptide as in Gjertsen et al.,

or a 9-mer or 10-mer peptide as in Ruppert et al. No specific guidance for selecting an exact sequence or size is provided by the cited references, or elsewhere in the art. Accordingly, a person in the art would not know how to reconcile the differences between the Gjertsen et al. and Ruppert et al. sequences to achieve the exact peptide YLVVVGADGV (5-14, 1Tyr-12Asp *ras*) that is Applicants' invention.

The '372 patent conflicts with both the Van Elsas et al. and the Gjertsen et al. references. First, the '372 patent used angiostatin and angiostatin peptides, whereas Van Elsas et al. and Gjertsen et al. used *ras* peptides. Second, the '372 patent used a 714-mer peptide, whereas Gjertsen et al. used a 17-mer peptide, and Van Elsas et al. used a 10-mer peptide. Third, the '372 patent suggested using K or Y, without specifying any position, whereas Van Elsas et al. and Gjertsen et al. used K at position 1. Thus, the '372 patent differs from the reports of Van Elsas et al. and Gjertsen et al. Without additional guidance, a person in the art would not know whether to use the size or sequence of the peptides reported by the '372 patent or the other two references. Accordingly, a person in the art would not know how to solve the differences among the '372 patent and the other references to achieve the exact 10-mer sequence YLVVVGADGV (5-14, 1Tyr-12Asp *ras*) that is Applicants' invention.

Therefore, the Ruppert et al. reference contradicts both the Van Elsas et al. and Gjertsen et al. references. In addition, the '372 patent contradicts both the Van Elsas et al. and Gjertsen et al. references. The solution to these conflicts is not found in the references themselves, or elsewhere in the art. Applicants respectfully note that the Examiner is required to give consideration where the teachings of 2 or more references are in conflict (MPEP §2143.01). Moreover, "it is improper to combine references where the references teach away from the

combination" *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). See MPEP §2145.

Conclusion: Ruppert et al., Van Elsas et al., and Gjertsen et al., and the '372 patent

Applicants' conclude that the Ruppert et al., Van Elsas et al., and Gjertsen et al. references and the '372 patent fail to teach or suggest construction of Applicants' exact peptide YLVVVGADGV (5-14, 1Tyr-12Asp *ras*). The cited references contradict each other and lead away from Applicants' invention. Thus, a person of skill in the art at the time the invention could not have used the combination of these references to make Applicants' invention. Only Applicants provide the teaching to construct the exact sequence YLVVVGADGV (5-14, 1Tyr-12Asp *ras*). It is noted that "[t]he references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention" *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182 n. 5 (Fed. Cir. 1986); MPEP §2141.01. Further:

> It is difficult but necessary that the decision maker forget what he or she has been taught...about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art who is presented ONLY with the references, and who is normally guided by the then-accepted wisdom in the art" *Gore v. Garlock*, 721 F.2d 1540 (emphasis added). See MPEP §2141.01.

When analysis is made without impermissible hindsight, it becomes clear that only Applicants teach the exact sequence YLVVVGADGV (5-14, 1Tyr-12Asp *ras*). The cited references fail to teach or suggest the subject matter of claims 10-15, 27, and 32. The claimed invention is therefore nonobvious in view of the cited references. Accordingly, withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

35 U.S.C. §103(a): Claims 25 and 66-67

Claims 25 and 66-67 have been rejected under 35 U.S.C. 103(a) as being obvious over Van Elsas et al. (1995) or Gjertsen et al. (1996) in view of Ruppert et al. (1993) or U.S. Patent No. 5,861,372 (1999) as applied to claims 10-15, 27 and 32 above, and further in view of U.S. Patent No. 6,039,948 (2000) (Office Action, page 4). Applicants respectfully traverse this rejection.

As supported by the facts, case law, and MPEP sections cited above, it is respectfully asserted that the primary references of Van Elsas et al., Gjertsen et al., Ruppert et al., and the '372 patent contradict each other and lead away from Applicants' invention. In particular:

The Van Elsas et al. reference

- *leads away* from the claimed invention by reporting that the KLVVVGADGV (5-14, 12Asp *ras*) peptide binds poorly to HLA-A*02021; and
- uses the preferred peptide species CLLDILDTAGL (51-61, 61Leu *ras*), which is *structurally different* from the claimed species of the invention;
- *conflicts* with the Ruppert et al. reference and the '372 patent regarding the sizes and sequences of the peptides;
- *conflicts* with Ruppert et al. regarding the effect of "favored residues" on HLA binding;

The Gjertsen et al. reference

- *leads away* from the claimed invention by reporting that the KLVVVGADGVGKSALTI (5-21, 12Asp *ras*) peptide produces no response or a non-specific immune response;
- *conflicts* with the Ruppert et al. reference and the '372 patent regarding the sizes and sequences of the peptides;

The Ruppert et al. reference

- *leads away* from the claimed invention by reporting that unfavored residues such as D have dominant negative effects on HLA-2.1 binding; this makes Applicants' results *unexpected and surprising*;
- fails to teach (in combination with the other references) the *exact, claimed sequence* YLVVVGADGV;
- *conflicts* with the Van Elsas et al. and Gjertsen et al. reference regarding the sizes and sequences of the peptides;
- *conflicts* with Van Elsas et al. regarding the effect of "favored residues" on HLA binding;

The '372 patent

- *leads away* from the claimed invention by using angiostatin or large angiostatin peptides;
- uses the preferred peptide species comprising 714 amino acids of murine angiostatin which is *structurally different* from the claimed species of the invention;
- fails to teach (in combination with the other references) the *exact, claimed sequence* YLVVVGADGV; and
- *conflicts* with the Van Elsas et al. and Gjertsen et al. references regarding the sizes and sequences of the peptides.

Thus, a person of skill in the art at the time the invention could not have used these references, alone or combined, to make Applicants' invention. Accordingly, the primary references fail to make obvious the subject matter of claims 25 and 66-67. The secondary reference of the '948 patent cannot stand on its own against the claims. Withdrawal of the rejection under 35 U.S.C. §103(a) is therefore respectfully requested.

35 U.S.C. §103(a): Claims 33, 68, and 70

Claim 33, 68, and 70 have been rejected under 35 U.S.C. §103(a) as being obvious over Van Elsas et al. (1995), or Gjertsen et al (1996) in view of Ruppert et al. (1993) or U.S. Patent No. 5,861,372 (1999) as applied to claims 10-15, 27 and 32 above and further in view of U.S.

Patent No. 5,800,810 (1998) (Office Action, page 4). Applicants respectfully traverse this rejection.

In accordance with the facts, case law, and MPEP sections cited above, it is respectfully asserted that the primary references of Van Elsas et al., Gjertsen et al., Ruppert et al., and the '372 patent contradict each other and lead away from Applicants' invention. In particular:

The Van Elsas et al. reference

- *leads away* from the claimed invention by reporting that the KLVVVGADGV (5-14, 12Asp *ras*) peptide binds poorly to HLA-A*02021; and
- uses the preferred peptide species CLLDILDTAGL (51-61, 61Leu *ras*), which is *structurally different* from the claimed species of the invention;
- *conflicts* with the Ruppert et al. reference and the '372 patent regarding the sizes and sequences of the peptides;
- *conflicts* with Ruppert et al. regarding the effect of "favored residues" on HLA binding;

The Gjertsen et al. reference

- *leads away* from the claimed invention by reporting that the KLVVVGADGVGKSALTI (5-21, 12Asp *ras*) peptide produces no response or a non-specific immune response;
- *conflicts* with the Ruppert et al. reference and the '372 patent regarding the sizes and sequences of the peptides;

The Ruppert et al. reference

- *leads away* from the claimed invention by reporting that unfavored residues such as D have dominant negative effects on HLA-2.1 binding; this makes Applicants' results *unexpected and surprising*;
- fails to teach (in combination with the other references) the *exact, claimed sequence* YLVVVGADGV;
- *conflicts* with the Van Elsas et al. and Gjertsen et al. reference regarding the sizes and sequences of the peptides;
- *conflicts* with Van Elsas et al. regarding the effect of "favored residues" on HLA binding;

The '372 patent

- *leads away* from the claimed invention by using angiostatin or large angiostatin peptides;
- uses the preferred peptide species comprising 714 amino acids of murine angiostatin which is *structurally different* from the claimed species of the invention;
- fails to teach (in combination with the other references) the *exact, claimed sequence* YLVVVGADGV; and
- *conflicts* with the Van Elsas et al. and Gjertsen et al. references regarding the sizes and sequences of the peptides.

Accordingly, a person of skill in the art at the time the invention could not have used the these references, alone or in combination, to make Applicants' invention. The primary references therefore fail to make obvious the subject matter of claims 33, 68, and 70. Regarding the secondary reference of the '948 patent, it is noted that Applicants are entitled to claim priority to parent application U.S. Serial No. 08/635,344, filed April 19, 1996 (see above). The filing date of the '948 patent is October 17, 1996. Therefore, the '948 patent cannot be used as a reference against the claims of the instant application. For all these reasons, withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

35 U.S.C. §103(a): Claim 34

Claim 34 stands rejected under 35 U.S.C. §103(a) as being obvious over Van Elsas et al. (1995) or Gjertsen et al. (1996) in view of Ruppert et al. (1993) or U.S. Patent No. 5,861,372 (1999) as applied to claims 10-15, 27 and 32-33, above, and further in view of U.S. Patent No. 6,001,349 (1999) (Office Action, page 5). Applicants respectfully traverse this rejection.

In view of the facts, case law, and MPEP sections cited above, it is respectfully asserted

that the primary references of Van Elsas et al., Gjertsen et al., Ruppert et al., and the '372 patent contradict each other and lead away from Applicants' invention. In particular:

The Van Elsas et al. reference

- *leads away* from the claimed invention by reporting that the KLVVVGADGV (5-14, 12Asp *ras*) peptide binds poorly to HLA-A*02021; and
- uses the preferred peptide species CLLDILDTAGL (51-61, 61Leu *ras*), which is *structurally different* from the claimed species of the invention;
- *conflicts* with the Ruppert et al. reference and the '372 patent regarding the sizes and sequences of the peptides;
- *conflicts* with Ruppert et al. regarding the effect of "favored residues" on HLA binding;

Gjertsen et al. reference

- *leads away* from the claimed invention by reporting that the KLVVVGADGVGKSALTI (5-21, 12Asp *ras*) peptide produces no response or a non-specific immune response;
- *conflicts* with the Ruppert et al. reference and the '372 patent regarding the sizes and sequences of the peptides;

The Ruppert et al. reference

- *leads away* from the claimed invention by reporting that unfavored residues such as D have dominant negative effects on HLA-2.1 binding; this makes Applicants' results *unexpected and surprising*;
- fails to teach (in combination with the other references) the *exact, claimed sequence* YLVVVGADGV;
- *conflicts* with the Van Elsas et al. and Gjertsen et al. reference regarding the sizes and sequences of the peptides;
- *conflicts* with Van Elsas et al. regarding the effect of "favored residues" on HLA binding;

The '372 patent

- *leads away* from the claimed invention by using angiostatin or large angiostatin peptides;

- uses the preferred peptide species comprising 714 amino acids of murine angiostatin which is *structurally different* from the claimed species of the invention;
- fails to teach (in combination with the other references) the *exact, claimed sequence* YLVVVGADGV; and
- *conflicts* with the Van Elsas et al. and Gjertsen et al. references regarding the sizes and sequences of the peptides.

As a result, a person of skill in the art at the time the invention could not have used these references, individually or in combination, to make Applicants' invention. Accordingly, the primary references fail to make obvious the subject matter of claim 34. The secondary reference of the '349 patent cannot stand on its own against the claims. Withdrawal of the rejection under 35 U.S.C. §103(a) is therefore respectfully requested.

SUMMARY

It is believed that the claims as presently amended are in condition for allowance. An action passing this case to issue is respectfully urged. In the event that the Examiner is of the opinion that further discussion of the application would be helpful, the Examiner is hereby respectfully requested to telephone Applicants' undersigned representative at (212) 415-8742 and is assured of full cooperation in an effort to advance the prosecution of the instant application and claims to allowance.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for the timely consideration of this amendment under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account No. 13-4500, Order No. 2026-4230US1. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

Dated: April 9, 2002

By: _____
Caryn DeHoratius
Registration No. 45,881

Correspondence Address:
MORGAN & FINNEGAN, L.L.P.
345 Park Avenue
New York, NY 10154-0053
(212) 758-4800 Telephone
(212) 751-6849 Facsimile

APPENDIX 1

AMENDED CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

34. The pharmaceutical composition according to claims 32 or 33, further comprising a liposome formulation, an antigen presenting cell, or an adjuvant comprising [a RIBI Detox™ formulation] mycobacterial cell wall skeleton and monophosphoryl lipid A.

APPENDIX 2

AMENDED PARAGRAPH WITH MARKINGS TO SHOW CHANGES MADE

On page 11, lines 30 to 35 through page 12, lines ° to 5:

At least one or more mutant *ras* peptides may be administered in a dose of about 0.05 mg to about 10 mg per vaccination of the mammal, preferably about 0.1 mg to about 5 mg per vaccination. Several doses may be provided over a period of weeks as indicated. In one embodiment a dose is provided every month for 3 months. The mutant *ras* peptide may be administered alone or in combination with adjuvants, in a liposome formulation, cytokines, biological response modifiers, or other reagents in the art that are known to enhance immune response. Adjuvants include but are not limited to RIBI Detox™ (comprising mycobacterial cell wall skeleton and monophosphoryl lipid A), QS21, alum and incomplete Freund's adjuvant. In one embodiment, the mutant *ras* peptide is administered in combination with Detox™ (RIBI Immunochem, Hamilton, MT).